

Influence of Fluoxetine on Olanzapine Pharmacokinetics

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Denis Gossen¹, Jean-Marie de Suray¹, Francois Vandenhende¹, Claude Onkelinx¹ and Diamon Gangji²

¹Lilly Research Laboratories, Lilly Development Centre, rue Granbonpre 11, B-1348 Mont-Saint-Guibert, Belgium

²Unité de Chimiotherapie, Hôpital Erasme, Université Libre de Bruxelles, route de Lennik 808, B-1070 Bruxelles, Belgium

ABSTRACT Conventional antidepressant treatment fails for up to 30% of patients with major depression. When there are concomitant psychotic symptoms, response rates are even worse. Thus, subsequent treatment often includes combinations of antidepressants or augmentation with antipsychotic agents. Atypical antipsychotic agents such as olanzapine cause fewer extrapyramidal adverse effects than conventional antipsychotics; for that reason, they are an advantageous augmentation strategy for treatment-resistant and psychotic depression. The purpose of this study was to assess the potential for pharmacokinetic interaction between olanzapine and fluoxetine, a popular antidepressant that is a selective serotonin reuptake inhibitor. The pharmacokinetics of 3 identical single therapeutic doses of olanzapine (5 mg) were determined in 15 healthy nonsmoking volunteers. The first dose of olanzapine was taken alone, the second given after a single oral dose of fluoxetine (60 mg), and the third given after 8 days of treatment with fluoxetine 60 mg, qd. Olanzapine mean C_{max} was slightly higher (by about 18%) and mean CL/F was slightly lower (by about 15%) when olanzapine was coadministered with fluoxetine in single or multiple doses. Olanzapine mean $t_{1/2}$ and median t_{max} did not change. Although the pharmacokinetic effects of fluoxetine on olanzapine were statistically significant, the effects were small and are unlikely to modify olanzapine's safety profile. The mechanism of influence is consistent with an inhibition of CYP2D6, which is known to control a minor pathway of olanzapine metabolism.

KEYWORDS: CYP2D6, Fluoxetine, Olanzapine, Pharmacokinetics, Drug Interaction

INTRODUCTION

Combination therapies of antipsychotic and antidepressant agents are increasingly used for difficult-to-treat mood disorders¹ because conventional antidepressant treatment fails for up to 30% of patients with major depressive disorder² and response rates decrease with concomitant psychotic symptoms. Atypical antipsychotic agents such as olanzapine cause fewer extrapyramidal adverse effects than conventional antipsychotics and are thus an advantageous antidepressant augmentation strategy for difficult-to-treat disorders such as treatment-resistant depression and depression with psychotic features.

***Corresponding author:** Francois Vandenhende, Lilly Research Laboratories, Lilly Development Centre, rue Granbonpre 11, B-1348 Mont-Saint-Guibert, Belgium. Telephone: +32 10 476402; Facsimile: +32 10 476475; E-mail: Francois@lilly.com

Olanzapine (molecular weight: 312.43) is a potent dopamine and serotonin antagonist with anticholinergic and antihistaminic activity. It is marketed under the trade name Zyprexa and is classified as an atypical antipsychotic agent.³ The major metabolite of olanzapine in the urine and plasma has been identified as the 10-N-glucuronide of olanzapine. Other metabolic pathways involve flavin-containing monooxygenases and at least 2 specific cytochrome P450 isoenzymes: CYP1A2 and CYP2D6.⁴

Fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI), is extensively metabolized in the liver to form norfluoxetine, an active metabolite, and other metabolites. It has been shown that fluoxetine and norfluoxetine inhibit CYP2D6 in liver tissue preparations.^{5,6} Because CYP2D6 is one of the pathways of olanzapine metabolism, and various metabolic pathways for fluoxetine may compete with those for olanzapine, fluoxetine might influence the pharmacokinetic profile of olanzapine. Because atypical antipsychotic and SSRI antidepressant drugs may be prescribed together, this study was conducted to evaluate the influence of fluoxetine, after single and repeated administration, on the pharmacokinetic characteristics of olanzapine after a single dose in healthy volunteers.

MATERIALS AND METHODS

Subjects

Subjects were nonsmokers who were of normal build and had no clinically significant abnormalities. They had not participated in other clinical trials or donated blood during the preceding 3 months or shown evidence of drugs of abuse in urine.

The Ethics Committee of the Hôpital Erasme (Brussels) reviewed the protocol and informed consent document. Prior to study initiation, all subjects signed the informed consent document, gave a full medical history, and underwent a physical examination. They were also subjected to the following tests and procedures: a 12-lead electrocardiogram, a standard electroencephalogram recording, and a battery of standard clinical laboratory tests. For female subjects, a pregnancy test was performed. No concurrent medications (including oral contraceptives) were allowed. The study was conducted following the principles of good clinical practice. Fifteen subjects (4 females and 11 males) completed the study.

Thirteen subjects were Caucasian, 3 were Hispanic, and one was Asian. Ages ranged from 23 to 40 years (mean = 32 ± 5 years). At admission, mean height was 173 ± 10 cm and mean weight was 71 ± 13 kg.

Study Design

This was an open-label, single-sequence crossover design comprising 3 treatment periods over 5 to 6 weeks. The subjects received the following treatments:

- Period 1, day 1: single dose of olanzapine 5 mg po.
- Period 2, day 1: single dose of fluoxetine 60 mg po followed 1 hour later by a single dose of olanzapine 5 mg po.
- Period 3, day 1 to day 8: fluoxetine 60 mg qd given po, and 1 hour after the last dose on day 8 a single dose of olanzapine 5 mg po. This dosing regimen was chosen in order to provide plasma concentrations on day 8 that approximate the steady-state values of a 20-mg daily dose regimen.⁷

After an 8-day regimen of 60 mg fluoxetine per day, the norfluoxetine-to-fluoxetine plasma concentration ratio does not mimic steady-state conditions but the circulating plasma concentrations of fluoxetine and norfluoxetine meet (norfluoxetine) or exceed (fluoxetine) typical steady-state values.

There was an interval of 10 days between olanzapine doses of periods 1 and 2, and at least 15 days between olanzapine doses of periods 2 and 3. During each period, the volunteers remained in the clinical pharmacology unit for 24 hours following the administration of olanzapine. After the administration of each dose of olanzapine, sequential blood samples were obtained at the following times relative to dose: 0 (predose), 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours.

Drug Measurements

Olanzapine was measured in plasma using high-performance liquid chromatography with electrochemical detection.⁸ The limit of quantification for olanzapine was 0.25 ng/mL. The average interday accuracy was 97%, with an average precision (% CV) of 3% over the concentration range of 0.25 to 100 ng/mL; fluoxetine and norfluoxetine did not cause significant interference in the quantification of olanzapine. Fluoxetine and norfluoxetine were determined in plasma by means of gas chromatography with electron-capture detection.⁹ The limit of quantification of fluoxetine and norfluoxetine was 1 ng/mL ($\cong 3$ nmol/L); olanzapine did not cause significant

interference in the quantification of fluoxetine or norfluoxetine.

Pharmacokinetic Analysis

The following pharmacokinetic parameters were calculated for olanzapine at each study period: C_{max} , t_{max} , $t_{1/2}$, AUC_{0-24h} , $AUC_{0-\infty}$, and apparent oral plasma clearance (CL/F). Pharmacokinetic analysis was performed using the Siphar/Win Program (version 1.2). Data were fitted using a weighted least squares means algorithm, and the half-life was derived from a nonlinear regression analysis on the terminal portion of the plasma concentration-time profile. Extrapolated $AUC_{t-\infty}$ did not exceed 15% of the total area (i.e., $AUC_{0-\infty}$). Fluoxetine and norfluoxetine concentrations were monitored during periods 2 and 3.

Statistical Methods

For all pharmacokinetic variables except t_{max} , treatment groups were compared using a repeated-measures analysis of variance (ANOVA). Prior to analysis, C_{max} , AUC_{0-24h} , $AUC_{0-\infty}$, and clearance were log transformed. Means (geometric means for log-transformed data) and variance estimates were extracted from the ANOVA model and used in constructing unadjusted 90% confidence intervals on mean differences (ratios for log-transformed data) between olanzapine administration with fluoxetine (periods 2 and 3) and without fluoxetine (period 1). The assessment of the lack of drug interaction was made by checking the inclusion of the 90% confidence intervals into a range defined as 80% to 120% (125% for log-transformed data) of the mean of period 1. For t_{max} , the differences between isolated (period 1) and single (period 2) or multiple (period 3) fluoxetine coadministration were tested with a Wilcoxon signed-rank test at the 5% level. The statistical computations were performed using the statistical package SAS.

RESULTS

Adverse Experiences

There were no serious or unexpected adverse events. Adverse events were of mild to moderate intensity. The most frequent symptoms were dry mouth ($n = 6$, shown by 2 subjects) and asthenia ($n = 4$, shown by 2 subjects) and were independent of period. Laboratory data obtained 5 days after olanzapine dosing, at each period, did not reveal any clinically significant changes in comparison with data obtained at admission. Vital signs changes remained within physiological normal variability

and none of the individual changes were regarded as clinically significant.

Pharmacokinetics

The main pharmacokinetic parameters of olanzapine are presented in Tables 1 and 2 for the 3 periods. Corresponding mean plasma concentration time curves are pictured in Figure 1. Mean plasma C_{max} data for fluoxetine and norfluoxetine were approximately 0.2 $\mu\text{mol/L}$ and

0.1 $\mu\text{mol/L}$ at period 2, and 0.9 $\mu\text{mol/L}$ and 0.5 $\mu\text{mol/L}$ at period 3, respectively. The main olanzapine pharmacokinetic parameters for the 3 study periods were submitted to ANOVA. After a single fluoxetine dose, the upper limits of the 90% confidence interval for C_{max} and $AUC_{0-\infty}$ were slightly above the 125% bound (129% for C_{max} and 126% for $AUC_{0-\infty}$), and the total clearance was slightly under the 80% bound (79% for total clearance). Graphical comparisons for C_{max} , $t_{1/2}$, and CL/F values by individual subject that contrast the data for periods 1, 2, and 3 are shown in Figure 2.

Table 1. Statistical Comparison of Olanzapine Pharmacokinetic Parameters Between Period 1 (Single Dose of Olanzapine) and Period 2 (Single Dose of Fluoxetine + Single Dose of Olanzapine)

PK Parameters*	Mean (% CV) Without Fluoxetine (Period 1)	Mean (% CV) With Single Fluoxetine (Period 2)	Ratio: Period 2 Period 1	90% Confidence Interval†	
				Lower Limit	Upper Limit
$AUC_{0-\infty}$ (ng·h/mL)	272 (41.7)	321 (40.1)	1.18	1.10	1.26‡
AUC_{0-24h} (ng·h/mL)	113 (32.5)	130 (32.3)	1.15	1.08	1.22
C_{max} (ng/mL)	7.6 (39.2)	9.0 (37.5)	1.18	1.08	1.29‡
CL/F (L/h)	18.4 (41.7)	15.6 (40.1)	0.85	0.79‡	0.91
$t_{1/2}$ (h)	32.2 (19.8)	32.3 (17.5)	1.00	0.91	1.09
t_{max} (h)§	3	3		Wilcoxon P value = .6436	

*AUC, C_{max} , and CL/F values were log transformed for the ANOVA analysis.

†If the confidence interval does not include 1.0, then there was a statistically significant change in the parameter.

‡Indicates values outside of the 80-120% or 80-125% range (based upon log-transformed data).

§For t_{max} , median values are reported and Wilcoxon signed-rank test was applied.

Table 2. Statistical Comparison of Olanzapine Pharmacokinetic Parameters Between Period 1 (Single Dose of Olanzapine) and Period 3 (Multiple Dose of Fluoxetine + Single Dose of Olanzapine)

PK Parameters*	Mean (% CV) Without Fluoxetine (Period 1)	Mean (% CV) With Multiple Fluoxetine (Period 3)	Ratio: Period 3 Period 1	90% Confidence Interval†	
				Lower Limit	Upper Limit
$AUC_{0-\infty}$ (ng·h/mL)	272 (41.7)	314 (50.0)	1.15	1.08	1.24
AUC_{0-24h} (ng·h/mL)	113 (32.5)	131 (37.1)	1.16	1.09	1.23
C_{max} (ng/mL)	7.6 (39.2)	8.8 (36.2)	1.15	1.06	1.26‡
CL/F (L/h)	18.4 (41.7)	15.9 (50.0)	0.87	0.81	0.93
$t_{1/2}$ (h)	32.2 (19.8)	31.2 (30.1)	0.97	0.88	1.06
t_{max} (h)§	3	3		Wilcoxon P value = .1953	

*AUC, C_{max} , and CL/F values were log transformed for the ANOVA analysis.

†If the confidence interval does not include 1.0, then there was a statistically significant change in the parameter.

‡Indicates values outside of the 80-120% or 80-125% range (based upon log-transformed data).

§For t_{max} , median values are reported and Wilcoxon signed-rank test was applied.

After single coadministration of fluoxetine, the C_{max} and $AUC_{0-\infty}$ of olanzapine increased by 18%, whereas the total apparent clearance decreased by 15%. At the end of a multiple administration of fluoxetine, all 90% confidence intervals fell within the equivalency range, with the only exception being C_{max} , for which the upper bound (126%) was slightly above the 125% limit. Olanzapine C_{max} was increased by 15% after multiple fluoxetine co-administration. The olanzapine half-life and t_{max} were unchanged after both single and multiple administrations of fluoxetine.

DISCUSSION

The slight decrease in olanzapine's apparent clearance observed in the presence of fluoxetine may be explained by the inhibitory effects of fluoxetine on CYP2D6. This enzyme plays a minor role in the metabolism of olanzapine. Fluoxetine concentrations after a single dose of fluoxetine 60 mg (period 2) and after 8 daily doses of fluoxetine 60 mg (period 3) are comparable in magnitude with the value of the CYP2D6 in vitro human liver microsomes inhibitory constant of fluoxetine and norfluoxetine (K_i 0.5 $\mu\text{mol/L}$).^{5,6} However, in vivo/in vitro comparisons are complex; other factors such as protein binding and plasma/tissue partitioning need to be considered. Nevertheless, fluoxetine has been shown in vivo to be an inhibitor of desipramine and imipramine metabolism under similar circumstances, and these effects are likely attributable to an inhibitory effect of fluoxetine on CYP2D6.⁷

Fluoxetine and norfluoxetine do not inhibit the CYP3A subfamily in vivo.¹⁰ The in vitro inhibitory constants for the effect of fluoxetine and norfluoxetine on CYP3A (K_i of about 20 and 65 $\mu\text{mol/L}$ for norfluoxetine and fluoxetine, respectively¹¹) suggest that it is unlikely that fluoxetine has any important effect on these enzymes. Furthermore, the CYP3A subfamily is likely not an important metabolic pathway of olanzapine.¹² Olanzapine clearance is induced by pretreatment with carbamazepine,¹³ but this likely involves effects on CYP1A2 or possibly other metabolic systems.⁴

The broad array of the potential effects of newer antidepressants on key cytochrome P450 enzyme systems has been reviewed by Nemerooff.¹⁴ Newer antidepressants and their metabolites are to some degree differentiated by their effects on CYP2D6, CYP1A2, CYP2C, or CYP3A and therefore may affect olanzapine to a different degree. For olanzapine, an effect on CYP1A2 like that caused by fluvoxamine has the potential to cause larger changes in olanzapine pharmacokinetics than those shown in this study, whereas other enzymes, specifically CYP2D6, CYP2C, or CYP3A, have much less or possibly no measurable impact on olanzapine.⁴

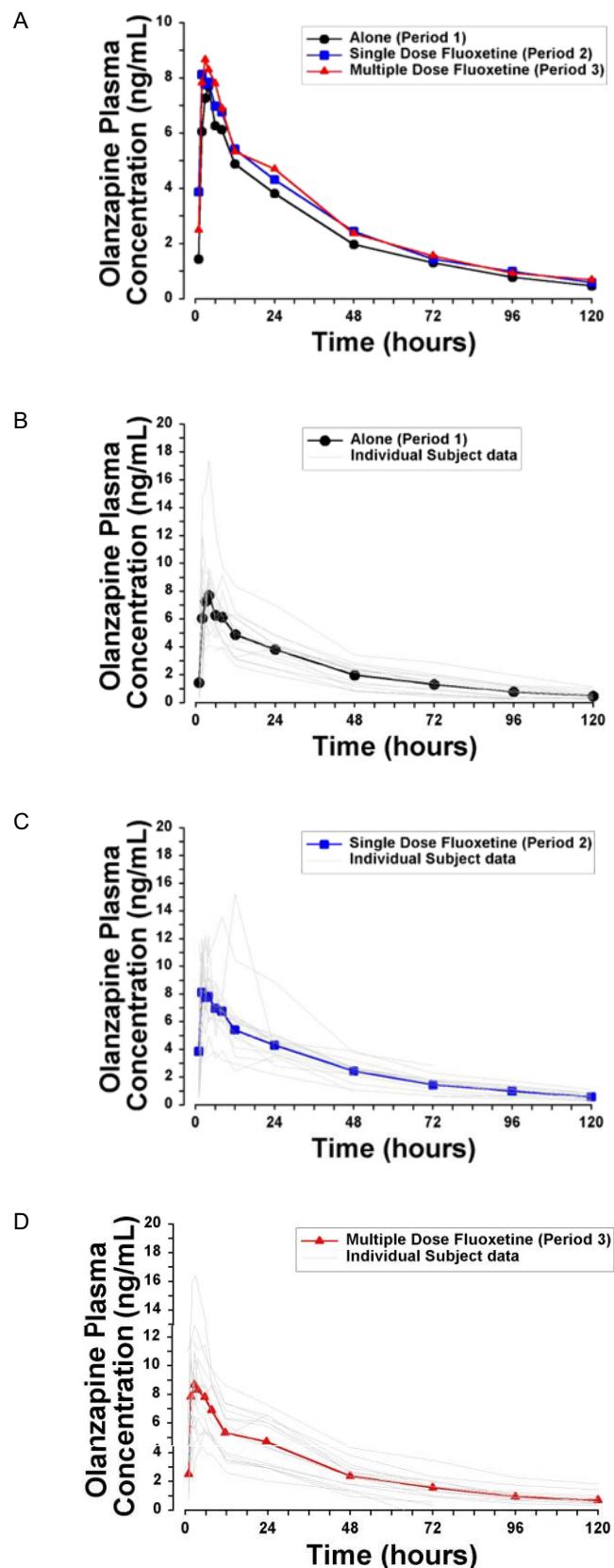
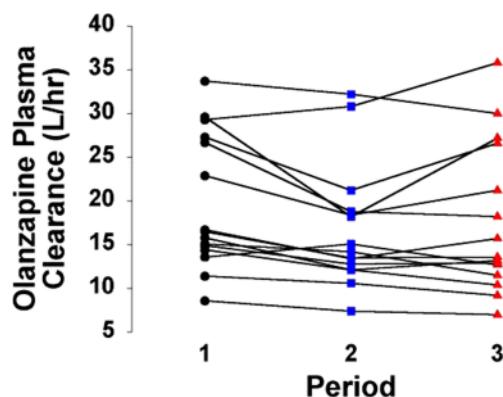
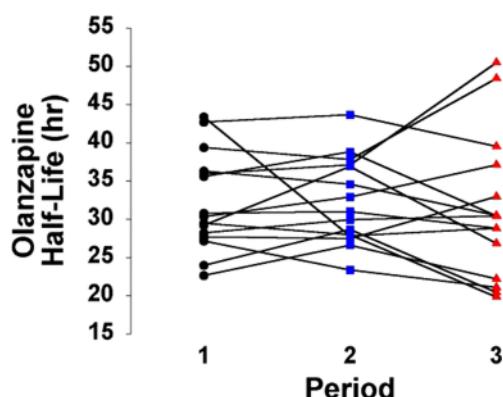


Figure 1. (A) Mean Olanzapine concentration values. (B) Olanzapine concentration, period 1. (C) Olanzapine concentration, period 2. (D) Olanzapine concentration, period 3.

A



B



C

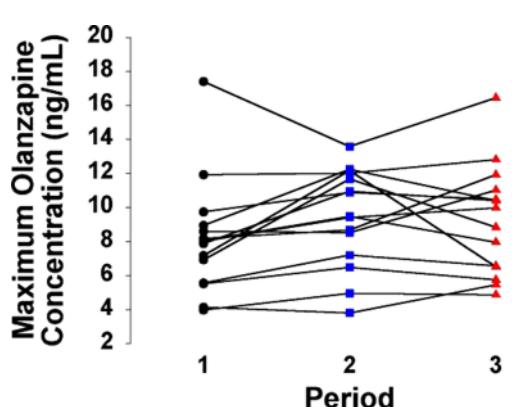


Figure 2. (A) Olanzapine clearance. (B) Olanzapine half-life. (C) Olanzapine C_{max}.

Callaghan⁴ provides a thorough overview of the pharmacokinetics and metabolism of olanzapine. The research summarized therein identifies CYP1A2 and glucuronyl transferase (UDPGT) as the primary metabolic pathways and shows that CYP2D6 is only a minor metabolic pathway. Correspondingly, Brosen¹⁵ reports that fluvoxamine (not fluoxetine, paroxetine, citalopram, or sertraline) is a potent inhibitor of CYP1A2 metabolic substrates. Thus, olanzapine does not interact with antidepressants that lack a potent effect on CYP1A2, as the results of this study indicate.

In conclusion, the concomitant administration of fluoxetine and olanzapine results in a small increase in olanzapine C_{max} and AUC_{0-∞} (about 18%) and a small decrease in olanzapine plasma clearance (about 15%). This may reflect the known inhibition of CYP2D6 by fluoxetine and the minor role of CYP2D6 in the overall metabolic scheme of olanzapine.⁴

These small changes, although statistically significant, are unlikely to be clinically relevant. To put the 15% olanzapine clearance decrease in perspective, for example, it is worth noting that olanzapine clearance is 30% lower in women than in men, but this gender-based difference—although twice as large as the effect of fluoxetine on olanzapine clearance—made no difference in olanzapine's effectiveness or in its recommended dosing regimen. Therefore, it is unlikely that fluoxetine modifies the safety profile of olanzapine when the 2 drugs are administered concomitantly.

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